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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,897	02/22/2000	DALIT BARKAN	BARKAN=2	7830

1444 7590 07/30/2002

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1642	17

DATE MAILED: 07/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/403,897	Barkan et al
Examiner	**Art Unit**
Karen Can lla	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2-9 and 28-39* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *9, 29, and 35* is/are allowed.

6) ☒ Claim(s) *2-8, 28, 30-34, and 36-39* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Arguments

1. Claims 2-9 and 28-39 are pending and under consideration.

2. The rejection of claims 2-8, 28, 30-34 and 36-39 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for leptin and leptin fusion proteins, does not reasonably provide enablement for leptin muteins, leptin receptor agonists, active fragments or fractions of anyone thereof, active analogs or derivatives of any thereof, and mixtures of any thereof as inhibitors of tumor cell proliferation is maintained for reasons of record. It has been stated in the original rejection of Paper No. 10, mailed February 28, 2001, that in order for the leptin to exert it effect of inhibiting the phosphorylation of insulin receptor substrate-1, it must bind to the leptin receptor to activate JAK-2 (see: Bjorbaek et al, J. of Biological Chemistry, 1997). The instant specification provides only examples and guidance for the use of leptin as an inhibitor of the phosphorylation of insulin receptor substrate-1. Although having an intact leptin protein fused to another protein would have a reasonable expectation of binding the leptin receptor and activating the JAK-2 in the same manner as leptin, one of skill in the art would not know what changes in the leptin sequence could be tolerated by the leptin receptor with respect to JAK-2 activation. Therefore, practice of this invention to the full scope of the claims would require undue experimentation to make and use substances other than leptin or leptin-fusion proteins. Further it is well known in the art that receptor antagonists need not share structural similarities. For instance, Maxadilan, a peptide derived from sand flies, is an agonist at the

pituitary cyclase-activating peptide type I receptor, but bears no structural homology to PACAP. Thus it is not possible to predict the structural requirement necessary to both bind to the leptin receptor and activate JAK-2 in the same manner as leptin. Stating that the broadly claimed agonists and fragments have at least 60% identity to leptin is not a disclosure of how to alter the amino acid sequence of leptin in order to obtain muteins, fragments or agonists that would function as claimed. Muteins are defined on page 8 of the specification, active fragment are defined on page 14 and agonists on pages 14-15. However the specification relies only on general definitions, and does not teach one of skill in the art how to alter the amino acid sequence of leptin in order to obtain a mutein, active fragment or agonist that would function as claimed.

3. All other rejections and objections as stated in Paper No. 10 are withdrawn.

Conclusion

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR

1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

July 29, 2002

L1 ANSWER 1 OF 1 MEDLINE
ACCESSION NUMBER: 1999367433 MEDLINE
DOCUMENT NUMBER: 99367433 PubMed ID: 10438479
TITLE: Functional characterization of structural alterations in the sequence of the vasodilatory peptide maxadilan yields a pituitary adenylate cyclase-activating peptide type 1 receptor-specific antagonist.
AUTHOR: Moro O; Wakita K; Ohnuma M; Denda S; Lerner E A; Tajima M
CORPORATE SOURCE: Shiseido Research Center, Yokohama, Kanagawa 223-8553, Japan.
CONTRACT NUMBER: RO1 AR42005 (NIAMS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, **(1999 Aug 13)** **274** (33) **23103-10.**
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AB Maxadilan is a vasodilatory peptide derived from sand flies that is an agonist at the pituitary adenylate cyclase-activating peptide (PACAP) type 1 receptor. Surprisingly, maxadilan does not share significant sequence homology with PACAP. To examine the relationship between structure and activity of maxadilan, several amino acid substitutions and deletions were made in the peptide. These peptides were examined in vitro for binding to crude membranes derived from rabbit brain, a tissue that expresses PACAP type 1 receptors; and induction of cAMP was determined in PC12 cells, a line that expresses these receptors. The peptides were examined in vivo for their ability to induce erythema in rabbit skin. Substitution of the individual cysteines at positions 1 and 5 or deletion of this ring structure had little effect on activity. Substitution of either cysteine at position 14 or 51 eliminated activity. Deletion of the 19 amino acids between positions 24 and 42 resulted in a peptide with binding, but no functional activity. The capacity of this deletion mutant to interact with COS cells transfected with the PACAP type 1 receptor revealed that this peptide was a specific antagonist to the PACAP type 1 receptor.